Workshop on Use of Radiolabeled Platelets for Assessment of *in vivo* Viability of Platelet Products
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FDA Current Approach to Evaluating Efficacy of Platelet Products

Salim Haddad, M.D.
Division of Hematology, OBRR
Center for Biologics Evaluation and Research

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Platelet Product Efficacy

- Ability to circulate
- Ability to prevent or stop bleeding

MAJOR CONCERNS ABOUT PLATELET EFFICACY

Hemostasis
Clinical trials →
- **Platelet substitutes**
- **Chemically modified platelets**

Radiolabeled
Studies →
- **New 5-7 day storage container**
- **New apheresis collection device**

In vitro studies on platelet
biochemistry and physiology → **Current storage condition**

MINIMAL CONCERNS ABOUT PLATELET EFFICACY

MAJOR CONCERNS ABOUT PLATELET EFFICACY

Hemostasis
Clinical trials → ▪ **Platelet substitutes**
▪ **Chemically modified platelets**

▪ New storage medium
▪ Extension beyond 7 days

Radiolabeled
Studies → ▪ **New 5-7 day storage container**
▪ **New apheresis collection device**

Minor modifications to current storage conditions

In vitro studies on platelet biochemistry and physiology → **Current storage condition**

MINIMAL CONCERNS ABOUT PLATELET EFFICACY

In Vitro Tests

- **Morphology**
  - **Enumeration, oil phase microscopy, MPV**
  - **Electron microscopy, platelet microparticles**

- **Biochemical status**
  - **pH, glucose, lactate, pO_2, pCO_2, HCO_3^-, LDH**
  - **ATP, mitochondrial uncouplers, dyes**

- **Platelet activation/ apoptosis**
  - **CD 62P (P-selectin)**
  - **PF3 , PF4, CD 63, β- thromboglobulin, PAC-1, Annexin V**

- **Physiologic responses**
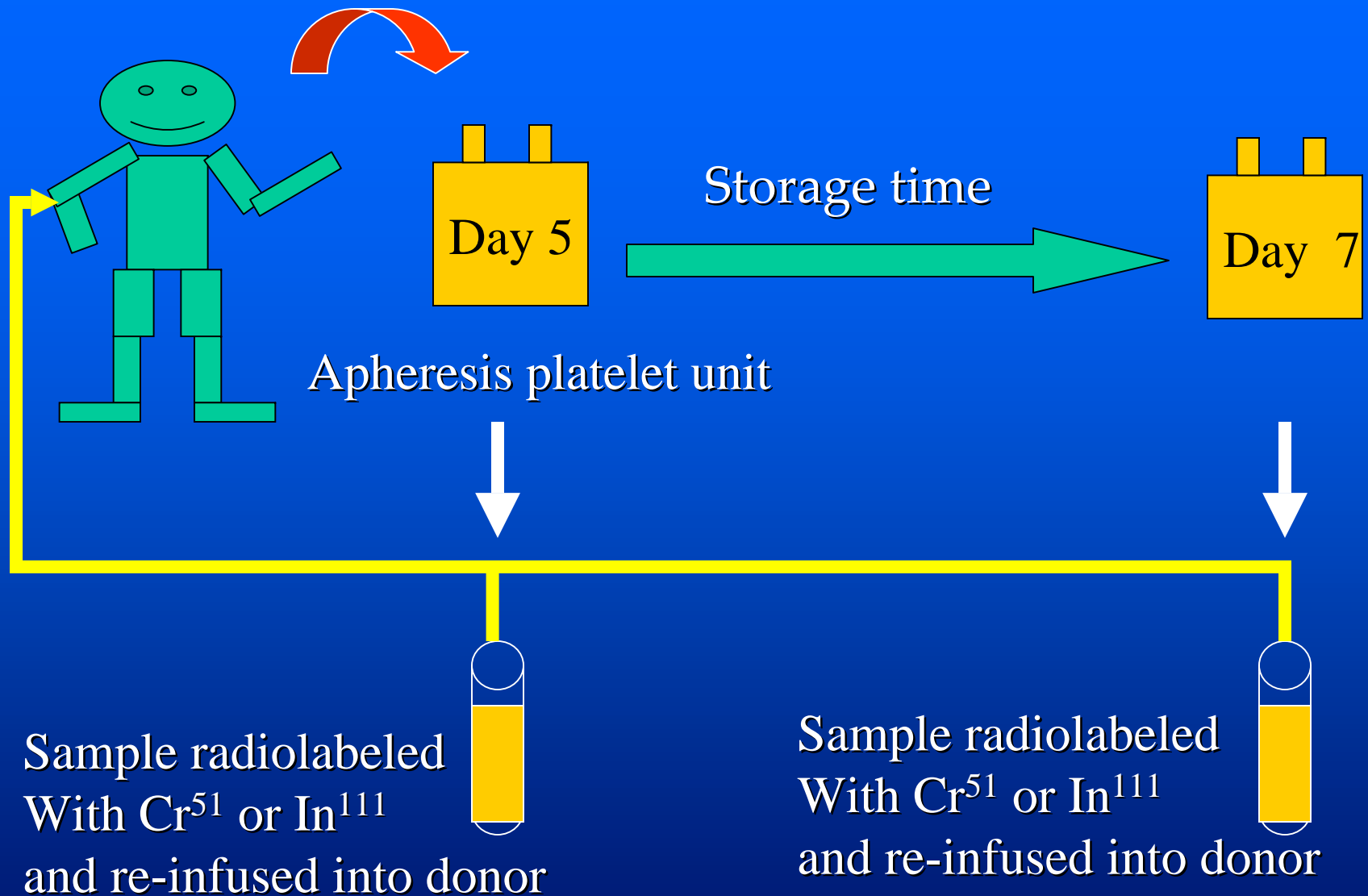 - **HSR, ESC**
  - **Aggregation studies, serotonin**

Supplemental

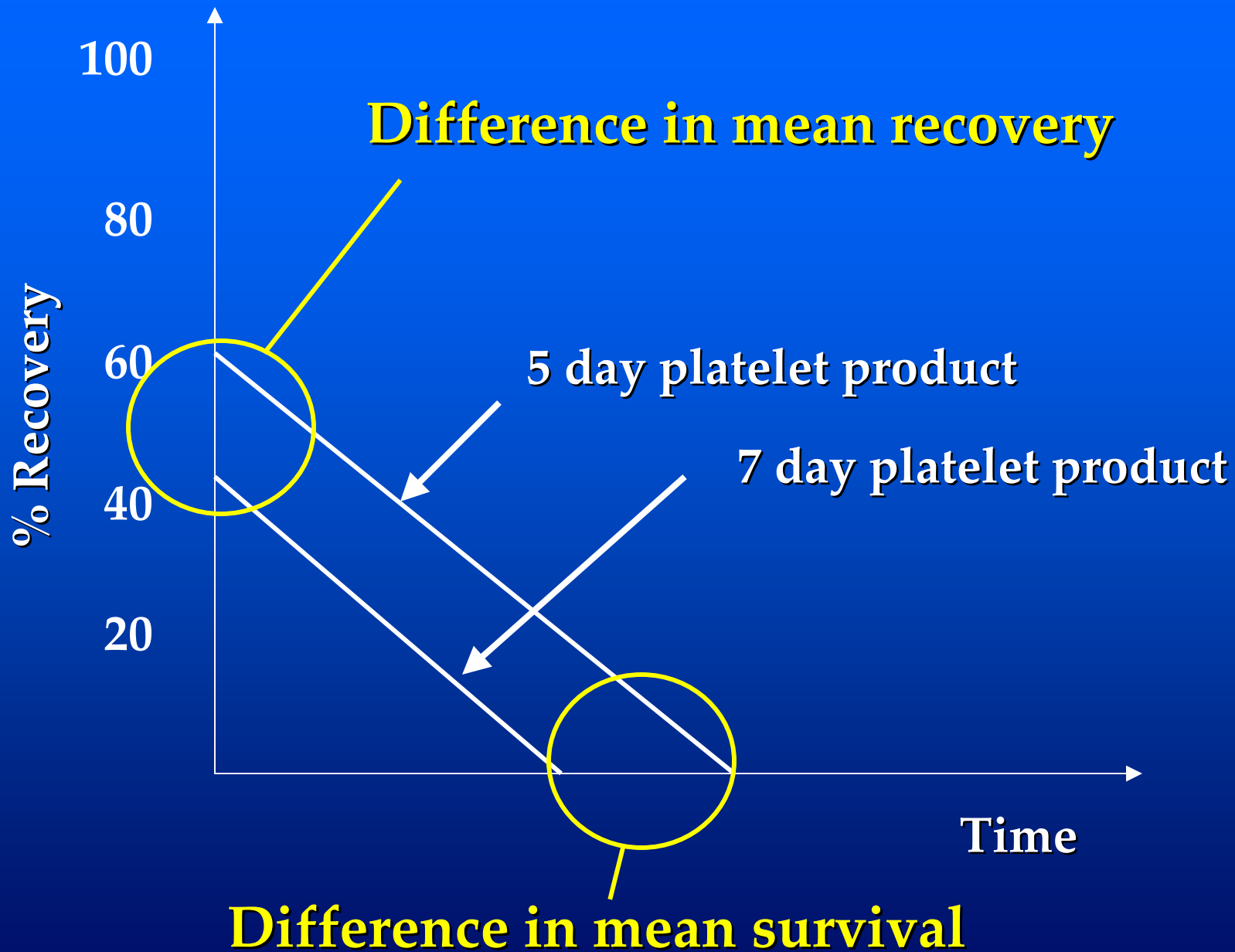# Correlation of *in vitro* testing with *in vivo* viability

- Poor
- pH, HSR, ESC
- Screening process
- Useful when used in conjunction with additional tests
- Quality check over time of process methodology

Platelet Survival in Circulation

- In vivo radiolabeling studies

- Autologous infusion in healthy volunteers
- Monitor recovery and survival of radiolabeled platelets in circulation in paired comparison of test and control products

Storage time

Day 5

Day 7

Apheresis platelet unit

Sample radiolabeled
With Cr^{51} or In^{111}
and re-infused into donor

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With Cr^{51} or In^{111}
and re-infused into donor

Problems with Current Approach to Radiolabeling Studies

- No minimum standard for platelet quality
- "Creeping inferiority"

Clinical Hemostatic Trials

- Randomized blinded phase III trials in thrombocytopenic patients
- Demonstrate participation of experimental product in actual hemostasis
- Primary endpoint: bleeding with experimental vs control platelets
- Safety endpoints
- Large and costly trials

Platelet Substitutes

- **Alternatives to liquid platelets stored at 22°C**
- **Challenging definition of efficacy**
- **Specific product goal**
- **In vitro with supplemental testing**
- **Animal tests**
  - Prothrombotic potential
  - Immunogenicity
  - Platelet additives toxicity
- **In vivo radiolabeling studies?**
- **Phase II: preliminary evidence of hemostatic efficacy, safety**
- **Phase III: safety and efficacy in proper population**

Summary Evaluation of Efficacy of New Platelet Products

- Modification to current collection, processing, storage : in vitro + radiolabeling studies

- Very novel methodologies: + hemostatic trials

- Possible post marketing studies

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